Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

Amendments to the Claims: .

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1   1.   (Currently amended) A method of modulating an Edg-2 receptor

2 mediated biological activity comprising contacting a cell expressing the Edg-2 receptor with an

3 amount of an modulator of the Edg-2 receptor sufficient to modulate the Edg-2 receptor

4 mediated biological activity wherein the modulator is a compound of the ~~structural formula (I)~~

5 Formula (I):
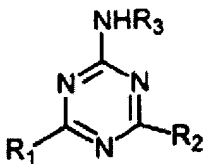
6

$$\underset{R_1}{\overset{NHR_3}{\diagup}}\ \text{triazine ring with } R_1,\ R_2$$

7   (I)

8 or a pharmaceutically ~~available~~ acceptable solvate or hydrate thereof, wherein;

9   each ~~of~~ R_1 and R_2 is a member independently selected from group consisting of -H, -halo,

10          $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$,

11          $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$,

12          $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl,

13          $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl,

14          $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, -OC(O)aryl, $-CO_2(CH_2)_mR_5$,

15   -N(OH)aryl, $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl,

16          $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$,

17          $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, ~~or~~ and

$$\text{—}\underset{}{\bigcirc}\!\!-(R_6)_p$$

18

1-SF/7373557.2

19   R_3 is <u>a member selected from the group consisting of</u> $-H$, $-C(R_5)_3$, $-(CH_2)_mOH$, $-C(O)R_5$,

20          $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl,

21          $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl,

22          $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_5-C_{10})$heteroaryl,

23   -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-N(OH)$aryl, $-NHC(O)R_5$,

24          $-NHC(O)OR_5$, $-NHC(O)NHR_5$, $-N=C($aryl$)$, -heterocylcoalkyl,

25          $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5$, $-OC(O)(CH_2)_mCHR_5R_5$,

26          $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, ~~or~~ <u>and</u>

27

28   wherein~~;~~

29   each R_5 and R_6 is <u>a member</u> independently <u>selected from the group consisting of</u>

30   -halo, $-NO_2$, $-CN$, $-OH$, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl,

31          $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl,

32          $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl),

33          $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl,

34          $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl,

35          $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle,

36          $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl,

37          $-NHC(O)NH(C_1-C_{10})$alkyl, $-NH($aryl$)$, $-N=C($aryl$)$,

38          $-OC(O)O(C_1-C_{10})$alkyl, ~~or~~ <u>and</u> $-SO_2NH_2$;

39   each m is independently an integer ranging from 0 to 8; and

40   each p is independently an integer ranging from 0 to 5.

1   **2.**   (Currently amended) A method of modulating an Edg-2 receptor

2   mediated biological activity in a subject comprising administering to the subject a

3   therapeutically effective amount of an modulator of the Edg-2 receptor wherein the modulator

4   is a compound of ~~the structural formula~~ Formula (II):
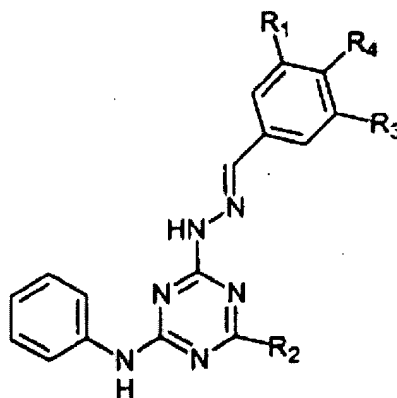
5

6   (II)

7   or a pharmaceutically ~~available~~ acceptable solvate or hydrate thereof, wherein~~;~~

8   each ~~of~~ R_1, R_2, $\underline{R_3}$ and R_4 is a member independently selected from the group consisting

9   of -H, -halo, $\underline{-OH}$, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$,

10               $-C(O)R_5$, $-C(O)NR_5R_5$; $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$,

11               $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl,

12               $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl,

13               $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl,

14               $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, -OC(O)aryl,

15               $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR_5R_5, $-OC(O)(CH_2)_mCHR_5R_5$,

16               $-CO_2(CH_2)_mCHR_5R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$; ~~or~~ and

17

18   wherein~~;~~

19   each R_5 and R_6 is a member independently selected from the group consisting of -halo,

20               $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl,

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

21   -C(O)(C$_1$-C$_{10}$)alkyl, -C(O)NH(CH$_2$)$_m$(C$_1$-C$_{10}$)alkyl, -OCF$_3$, -benzyl,

22   -CO$_2$(CH$_2$)$_m$CH((C$_1$-C$_{10}$)alkyl(C$_1$-C$_{10}$)alkyl), -CO$_2$(C$_1$-C$_{10}$)alkyl, -(C$_1$-C$_{10}$)alkyl,

23   -(C$_2$-C$_{10}$)alkenyl, -(C$_2$-C$_{10}$)alkynyl, -(C$_3$-C$_{10}$)cycloalkyl, -(C$_8$-C$_{14}$)bicycloalkyl,

24   -(C$_5$-C$_{10}$)cycloalkenyl, -(C$_5$)heteroaryl, -(C$_6$)heteroaryl, -phenyl, naphthyl,

25   -(C$_3$-C$_{10}$)heterocycle, -CO$_2$(CH$_2$)$_m$(C$_1$-C$_{10}$)alkyl, -CO$_2$(CH$_2$)$_m$H,

26   -NHC(O)(C$_1$-C$_{10}$)alkyl, -NHC(O)NH(C$_1$-C$_{10}$)alkyl, -NH(aryl), -N=C(aryl),

27   -OC(O)O(C$_1$-C$_{10}$)alkyl, ~~or~~ and -SO$_2$NH$_2$;

28   each m is independently an integer ranging from 0 to 8; and

29   each p is independently an integer ranging from 0 to 5.

1   **3.**   (Original) The method of Claim **1** or **2**, wherein the modulator is an

2   agonist.

1   **4.**   (Original) The method of Claim **1** or **2**, wherein the modulator is an

2   antagonist.

1   **5.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 200 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

1   **6.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 40 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

1   **7.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 12 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

1   **8.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 5 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

1   **9.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 20 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

1   **10.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 200 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

1   **11.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 40 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

1   **12.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 12 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

1   **13.**   (Original) The method of Claim **1** or **2**, wherein the modulator exhibits at

2   least about 5 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

1   **14.**   (Original) The method of Claim **1** or **2**, wherein the biological activity is

2   cell proliferation.

1   **15.**   (Original) The method of Claim **14**, wherein the modulator exhibits at

2   least about 200 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

1   **16.**   (Original) The method of Claim **14**, wherein the modulator exhibits at

2   least about 5 fold inhibitory selectivity for Edg-2 relative to other Edg receptors.

1   **17.**   (Original) The method of Claim **14**, wherein the modulator exhibits at

2   least about 200 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

1   **18.**   (Original) The method of Claim **14**, wherein the modulator exhibits at

2   least about 5 fold inhibitory selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors.

1   **19.**   (Currently amended) The method of Claim **14**, wherein cell proliferation

2   leads to <u>cancer selected from the group consisting of</u> ovarian cancer, peritoneal cancer,

3   endometrial cancer, cervical cancer, breast cancer, colon cancer ~~or~~ <u>and</u> ~~prostrate~~ <u>prostate</u>

4   cancer.

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

1   **20.** (Original) The method of Claim **14**, wherein cell proliferation is

2   stimulated by LPA.

1   **21.** (Currently amended) The method of Claim **1** or **2**, wherein the biological

2   activity is <u>selected from the group consisting of</u> calcium mobilization, VEGF synthesis, IL-8

3   synthesis, platelet activation, cell migration, phosphoinositide hydrolysis, inhibition of cAMP

4   formation, actin polymerization, apoptosis, angiogenesis, inhibition of wound healing,

5   inflammation, cancer invasiveness, supressing autoimmune responses, ~~or~~ <u>and</u> atherogenesis.

1   **22.** (Currently amended) The method of Claim **1** or **2** wherein the modulator

2   binds to the Edg-2 receptor with a binding constant of at least about 10 ~~nm~~ <u>nM</u>.

1   **23.** (Currently amended) The method of Claim **1** or **2** wherein the modulator

2   binds to the Edg-2 receptor with a binding constant between about <u>100 fM and</u> 1 pM<u>.</u> ~~and 100~~

3   ~~fM.~~

1   **24.** (Original) The method of Claim 1 or **2**, wherein the modulator is a

2   nucleic acid, protein or carbohydrate.

1   **25.** (Original) The method of Claim **1** or **2**, wherein the modulator is an

2   organic molecule of molecular weight of less than 750 daltons.

1   **26.** (Currently amended) The method of Claim **1**, wherein the cell is a

2   <u>selected from the group consisting of</u> hepatoma cell, an ovarian cell, an epithelial cell, a

3   fibroblast cell, a neuronal cell, a carcinoma cell, a pheochromocytoma cell, a myoblast cell, a

4   platelet cell ~~or~~ <u>and</u> a fibrosarcoma cell.

1   **27.** (Currently amended) The method of Claim **21**, wherein the cell is

2   selected <u>from the group consisting of</u> OV2O2 human ovarian cell, a HTC rat hepatoma cell, a

3   CAOV-3 human ovarian cancer cell, MDA-MB-453 breast cancer cell, MDA-MB-231 breast

4   cancer cell, HUVEC cells A431 human epitheloid carcinoma cell ~~or~~ <u>and</u> a HT-1080 human

5   fibrosarcoma cell.

1-SF/7373557.2

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

1   **28.**   (Currently amended) The method of Claim ~~25~~ 1 or 2, wherein the

2   modulator ~~is a compound of~~ has a formula selected from ~~structural formula (III)~~:

127

3   ; and

131

4
5
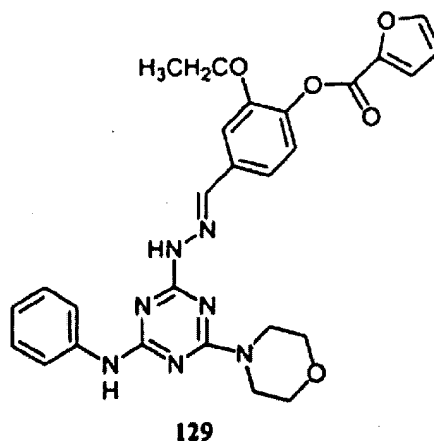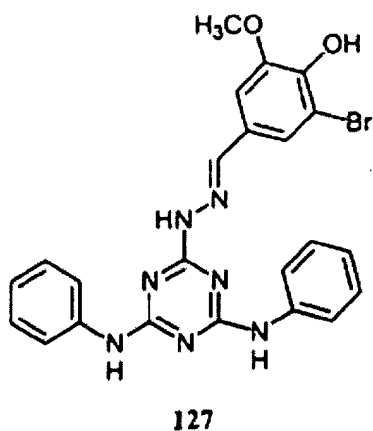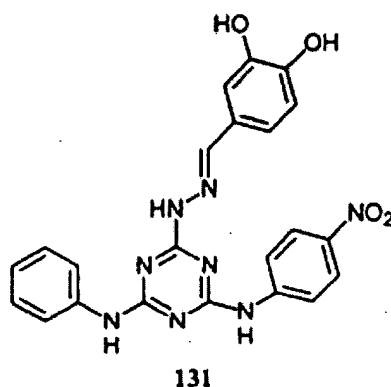
1   **29.**   (Currently amended) A method for treating or preventing a disease or

2   condition selected from cancers, acute lung diseases, acute inflammatory exacerbation of

3   chronic lung diseases, surface epithelial cell injury, ~~or~~ and cardiovascular diseases in a patient

4   in need of said treatment or said prevention, said method comprising administering to ~~a~~ said

5   patient ~~in need of such treatment or prevention~~ a therapeutically effective amount of a

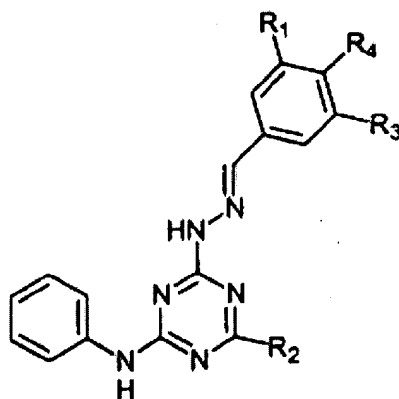6   compound of ~~structural formula~~ Formulae (I) or (II).

1   **30.**   (Currently amended) A method for treating or preventing a disease or

2   condition selected from ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer,

3   breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid

Page 8 of 15

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

4   cancer, lung cancer, kidney cancer, pancreas cancer, ~~prostrate~~ prostate cancer, adult respiratory

5   distress syndrome (ARDS), asthma, transcorneal freezing, cutaneous burns, ischemia ~~or~~ and

6   ~~artheselerosis~~ atherosclerosis in a patient in need of said treatment or said prevention, said

7   method comprising administering to ~~a~~ said patient ~~in need of such treatment or prevention~~ a

8   therapeutically effective amount of a compound of ~~structural formula~~ Formulae (I) or (II).

1   **31.**   (Currently amended) A method for treating or preventing a disease or

2   condition selected from cancers, acute lung diseases, acute inflammatory exacerbation of

3   chronic lung diseases, surface epithelial cell injury, ~~or~~ and cardiovascular diseases in a patient

4   in need of said treatment or said prevention, said method comprising administering to ~~a~~ said

5   patient ~~in need of such treatment or prevention~~ a therapeutically effective amount of a

6   compound of ~~structural formula~~ Formulae (I) or (II) and one or more agonists or antagonists of

7   an Edg-2 receptor.

1   **32.**   (Currently amended) A method for treating or preventing a disease or

2   condition selected from cancers, acute lung diseases, acute inflammatory exacerbation of

3   chronic lung diseases, surface epithelial cell injury, ~~or~~ and cardiovascular diseases in a patient

4   in need of said treatment or said prevention, said method comprising administering to ~~a~~ said

5   patient ~~in need of such treatment or prevention~~ a therapeutically effective amount of a

6   compound of ~~structural formula~~ Formulae (I) or (II) and one or more drugs useful in treating or

7   preventing cancers, acute lung diseases, acute inflammatory exacerbation of chronic lung

8   diseases, surface epithelial cell injury, or cardiovascular diseases.

1   **33.**   (New) A method of treating cancer in a patient comprising:

2   administering to the patient a therapeutically effective amount of a modulator of an Edg-2

3   receptor wherein the modulator is a compound of Formula (II):

4

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

(II)

7   or a pharmaceutically acceptable solvate or hydrate thereof, wherein

8   each R_1, R_2, R_3 and R_4 is a member independently selected from the group consisting of

9   -H, -halo, -OH, $-NO_2$, -CN, $-C(R_5)_3$, $-(CH_2)_mOH$, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$,

10    $-C(O)R_5$, $-C(O)NR_5R_5$; $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$,

11    $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl,

12    $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl,

13    $-(C_5-C_{10})$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -N(OH)aryl,

14    $-NHC(O)R_5$, $-NHC(O)OR_5$, $-NHC(O)NHR_5$, -heterocylcoalkyl, -OC(O)aryl,

15    $-(C_1-C_{10})$alkylNHC(O)$(CH_2)_mR_5$, $-(C_1-C_{10})$alkylNR$_5$R$_5$,-OC(O)$(CH_2)_m$CHR$_5$R$_5$,

16    $-CO_2(CH_2)_m$CHR$_5$R$_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, and

18   wherein

19   each R_5 and R_6 is a member independently selected from -halo, $-NO_2$, -CN, -OH, $-CO_2H$,

20    $-N(C_1-C_{10})$alkyl(C_1-C_{10})alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl,

21    $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl,

22    $-CO_2(CH_2)_m$CH$((C_1-C_{10})$alkyl(C_1-C_{10})alkyl$)$, $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl,

1-SF/7373557.2

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

23   -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl,

24   -$(C_5$-$C_{10})$cycloalkenyl, -(C_5)heteroaryl, -(C_6)heteroaryl, -phenyl, naphthyl,

25   -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m(C_1$-$C_{10})$alkyl, -$CO_2(CH_2)_mH$,.

26   -$NHC(O)(C_1$-$C_{10})$alkyl, -$NHC(O)NH(C_1$-$C_{10})$alkyl, -NH(aryl), -N=C(aryl),

27   -$OC(O)O(C_1$-$C_{10})$alkyl, and -SO_2NH_2;

28   each m is independently an integer ranging from 0 to 8; and

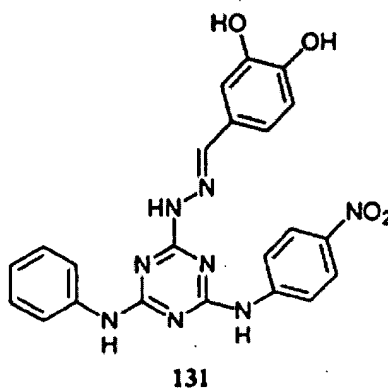29   each p is independently an integer ranging from 0 to 5.

1   **34.**   (New) The method of claim 33, wherein R_4 is an –OH group.

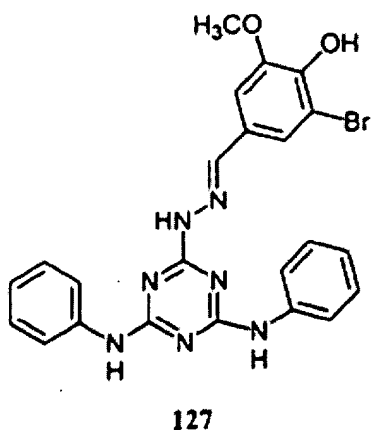1   **35.**   (New) The method of claim 34, wherein R_2 is

2
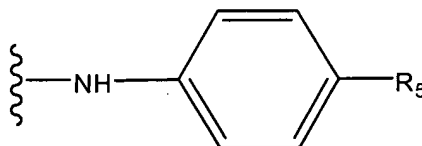
3   wherein R_5 is selected from H and NO_2.

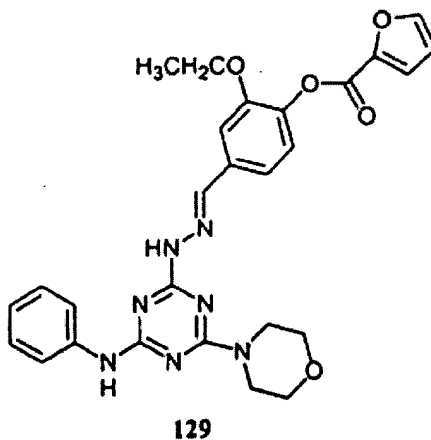1   **36.**   (New) The method of claim 35, wherein said compound has the formula:

131

2

1   **37.**   (New) The method of claim 35, wherein said compound has the formula:

Appl. No. 10/760,063
Amdt. dated October 24, 2006
Office Action dated April 25, 2006

PATENT

127

2

1   **38.**   (New) The method of claim **33**, wherein said compound has the formula:

2

129

3

1   **39.**   (New) The method of claim **33**, wherein said cancer is selected from the

2   group consisting of ovarian cancer, peritoneal cancer, endometrial cancer, cervical cancer,

3   breast cancer, colorectal cancer, uterine cancer, stomach cancer, small intestine cancer, thyroid

4   cancer, lung cancer, kidney cancer, pancreas cancer and prostate cancer.